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EXAMINER	
NIEBAUER, RONALD T	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,998	COOL ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-16,19* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-14,16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments and arguments filed 6/24/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn. Briefly, applicants amendments have overcome the previous 102 and 103 rejections. It is noted that claims 3,5-8 have been amended to recite ammonium, phosphonium, and sulfonium salts. Claims 9,12 have been amended to depend from a different claim.

Previously, (9/30/08) applicants elected a benzyltrimethylammonium salt and Fmoc protecting group. In the instant case, each of the elected species was found in the prior art or found to be obvious based on the prior art. Any art that was uncovered in the course of searching for the elected species that reads on non-elected species is also cited herein. In accord with section 803.02 of the MPEP, the Markush-type claims have been examined with respect to the elected species and to the extent necessary to determine patentability.

Since applicant elected Fmoc, claims 14-15 do not read on the elected species. Since the art cited below reads on claim 14, claim 14 is included in the instant rejection.

Claim 15 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/30/08.

Claims 1-2,17-18 have been cancelled.

Claims 3-14,16,19 are under consideration.

Claim Objections

This objection is necessitated by applicants addition of claim 19.

Claim 19 is objected to because of the following informalities: claim 19 recites 'synthesising'. However, the correct spelling of the word is 'synthesizing'.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim 12 was previously rejected under 112 2nd. Although the claim has been amended, the claim remains indefinite.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 refers to a salt addition step of steps a, b, or c of claim 3. However, claim 3 does not expressly recite a salt addition step in steps a, b, or c. Thus, there is insufficient antecedent basis for this limitation in the claim. It is noted that claim 3 refers to the use of a salt in the process. However, a use in the process is not the equivalent of using the salt in steps a, b, or c. Since claim 3 uses 'comprising' language the salt can be added prior to step a or after step c. Thus, it is unclear if the salt referred to in claim 12 is the same salt that is recited in claim 3. As such, it is unclear if one or two salts are required.

Claim Rejections - 35 USC § 102

The below rejections are new rejections necessitated by applicants amendments.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3-4,7,12-14,16,19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hudson (US 4,888,385).

Hudson teach using benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) during solid phase peptide synthesis (abstract, claim 1). Hudson teach the general solid phase peptide synthesis strategy (column 1) including deprotecting the alpha-amine group of the amino acid (column 1 line 28-29), washing (column 1 line 30), followed by addition of an alpha-amine protected amino acid (column 1 line 31-32), and repetition of the steps (column 1 lines 40-41) and cleavage (column 1 line 51). Hudson teach that the benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) is utilized when the amino acid is coupled (column 8 lines 26-32,38-42) and that solvents such as DMF (dimethylformamide) are used (column 8 line 31). In example 3 (column 9-10) Hudson teach the use of Fmoc protected amino acids and that DMF (dimethylformamide) was used as the solvent. Hudson also teach the use of Boc as a protecting group (column 1 line 26).

Since Hudson teach the general solid phase peptide synthesis strategy (column 1) including deprotecting the alpha-amine group of the amino acid (column 1 line 28-29), washing (column 1 line 30), followed by addition of an alpha-amine protected amino acid (column 1 line 31-32), and repetition of the steps (column 1 lines 40-41) steps a-c/a-d of claims 3-4,7 are met. Since Hudson teach that the benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) is utilized when the amino acid is coupled (column 8 lines 26-32,38-42) a phosphonium salt is used as recited in the claims, specifically at step c as recited in claim 7. In example 3 (column 9-10) Hudson teach the use of Fmoc protected amino acids. Hudson also teach the use of Boc as a protecting group (column 1 line 26). Thus the limitations of claims 13-14 are met. Hudson teach the general solid phase peptide synthesis strategy including repetition of the steps (column 1 lines 40-41) and cleavage (column 1 line 51) thus the limitations of claim 16 are met. It is noted that claim 19 states that there is no wash step between step a and b. It is noted that step b refers to claim 3 which includes a wash step. As such, the wash step as described by Hudson meets the limitations of claim 16b and there is not a wash step between step a and b as recited in claim 19. It is noted that claim 3 excludes certain solvents. In example 3 (column 9-10) Hudson teach the use of DMF (dimethylformamide) as the solvent.

It is noted that the claims state that the washing is 'thorough'. 'Thorough' is defined (page 2 of specification) as effective to remove reagents from the previous step. Since Hudson teach effective synthesis of peptides (see example 3 columns 9-10) the washings are necessarily thorough to allow for effective synthesis.

Although unclear (see 112 2nd) claim 12 has been interpreted such that a single salt is required and that salt can be added at any stage of the process as recited in claim 3. Hudson teach washing (column 1 line 30) thus the claim limitations are met.

Claims 3-4,9-12,16 are rejected under 35 U.S.C. 102(b) as being anticipated by Birr (US 4,290,943).

Birr teach methods of preparing polypeptides (abstract). Birr teach that peptides are prepared by solid phase technique (column 1 line 47-50). Birr specifically teach that the N-terminal protective group is removed (column 5 line 19-22), a wash is performed (column 5 line 29-30), and the next N-terminally protected amino acid is coupled (column 5 line 30-32). In a specific example (columns 6-8) Birr teach that benzyltrimethylammonium hydroxide (in methanol and dioxane) is used to cleave off a peptide fragment (column 7 lines 34-36).

Since Birr teach a solid phase technique (column 1 line 47-50) in which the N-terminal protective group is removed (column 5 line 19-22), a wash is performed (column 5 line 29-30), and the next N-terminally protected amino acid is coupled (column 5 line 30-32) steps a-c/a-d of claims 3-4 are met. Since Birr teach teach that benzyltrimethylammonium hydroxide (in methanol and dioxane) is used to cleave off a peptide fragment (column 7 lines 34-36) a salt is used in the process and the salt meets the limitations as recited in claims 9-11 of the instant claims. Birr teach a specific example (columns 6-8) in which a peptide is cleaved (column 7 lines 34-36), thus the limitations of claim 16 are met. It is noted that claim 19 states that there is no wash step between step a and b. It is noted that step b refers to claim 3 which includes a wash

step. As such, the wash step as described by Birr meets the limitations of claim 16b and there is not a wash step between step a and b as recited in claim 19.

It is noted that the claims state that the washing is 'thorough'. 'Thorough' is defined (page 2 of specification) as effective to remove reagents from the previous step. Since Hudson teach effective synthesis of peptides (see example 3 columns 9-10) the washings are necessarily thorough to allow for effective synthesis.

Although unclear (see 112 2nd) claim 12 has been interpreted such that a single salt is required and that salt can be added at any stage of the process as recited in claim 3. Birr teach washing (column 5 line 29-30) thus the claim limitations are met.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-6,8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mihala et al (Journal of Peptide Science 'An alternative solid phase peptide fragment condensation protocol with improved efficiency' 7:565-568 (2001)) and Thaler et al (Helvetica Chimica Acta v74 1991 pages 628-643 as cited with office action dated 1/23/09).

Mihala teach solid phase peptide synthesis (title). Mihala teach that the success of solid phase synthesis is limited by the aggregation of the growing peptide chains (abstract, page 565). Mihala teach that protected amino acids (page 566 section 'general') were used and that coupling steps were carried out with TBA*ODhbt (page 566 section 'solid phase synthesis') in chloroform-phenol. Mihala teach that TBA*ODhbt is a tetrabutyl ammonium salt which is used to enhance solubility (page 567 first complete paragraph). Mihala teach that the tetrabutyl ammonium salt additive lead to improved efficiency (title, abstract, Table 1).

Mihala teach the use of the ammonium salt additive with the coupling step, not with any other specific steps as recited in claims 5-6,8.

Mihala teach that the success of solid phase synthesis is limited by the aggregation of the growing peptide chains (abstract, page 565). Thaler also teach that a problem in solid phase synthesis is insufficient solvation which can lead to aggregation (page 628). Thaler teach that salt additives can increase resin swelling and improve coupling yields (Figure 4). Thaler

acknowledge that salt additives should be adjusted for the best results (conclusions page 639). Thaler specifically teach the use of salts for the washing and coupling steps (page 640 section 2).

Both Mihala and Thaler recognize aggregation of the growing peptide chain as a problem of solid phase peptide synthesis. From the teachings of Thaler one would recognize that the goal is to use salt additives to help solvation and to aid in preventing protein aggregation. Mihala teach the use of an ammonium salt improves efficiency of peptide synthesis. Since Thaler teach that salt additives help salvation and aid in preventing protein aggregation one would be motivated to use the ammonium salt taught by Mihala throughout the process. One would recognize that insufficient solvation and aggregation are possible at all steps of the solid phase synthetic process. As such, one would be motivated to include the ammonium salt in the solutions that are used in all steps of the solid phase synthesis including the deprotection steps.

Taken together, the solid phase synthesis steps are known in the art. Thaler teach deprotecting (i.e. cleaving), washing, and coupling of protected groups (see page 620 section 2, for example Boc-Ala). Mihala teach that protected amino acids (page 566 section 'genera') were used and that coupling steps were carried out with TBA*ODhbt (page 566 section 'solid phase synthesis'). Thus one would be motivated to carry out steps a-d of claims 5-6,8 of the instant claims. Further, using the ammonium salt as taught by Mihala at all steps of the process meets the specific salt limitations of claims 5-6,8 of the instant claims.

Since Thaler teach that salt additives can increase resin swelling and improve coupling yields (Figure 4) one would have a reasonable expectation of success. Since Mihala teach that the ammonium salt improves reaction efficiency one would have a reasonable expectation of success. The claims would have been obvious because the technique for improving solid phase

synthesis by including salts at specific steps (for example, during deprotection) was part of the ordinary capabilities of a person of ordinary skill in the art, in view of teaching of the technique for improving solid phase synthesis at other steps (for example, during coupling and washing). Further, one would be motivated to optimize the process as taught by Thaler (conclusions page 639).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference.

Conclusion

It is noted that claims 3,5-8 have been amended to recite ammonium, phosphonium, and sulfonium salts. Claims 9,12 have been amended to depend from a different claim. Claim 19 has been added as a new claim. As such, applicants amendments have necessitated the new grounds of rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

/Ronald T Niebauer/
Examiner, Art Unit 1654